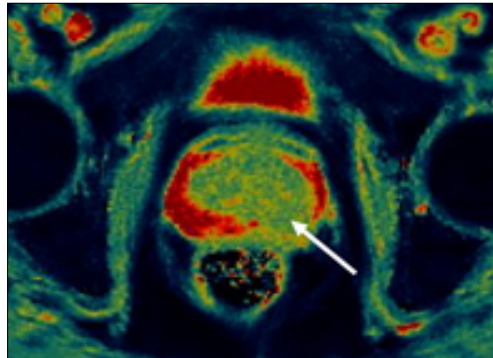


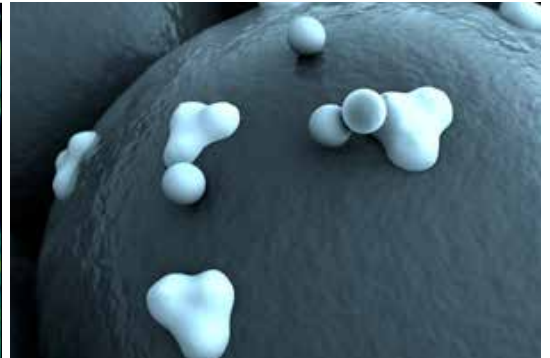
INNOVATIONS IN CANCER



3
Repurposing
Bortezomib



4 - 5
The Prostate Project



7
Diagnosing Dysfunction

A MESSAGE From the Director

High-Tech and
High-Touch

Excellence in cancer care is both high-tech and high-touch, the fusion of scientific discovery with humane application into new and effective therapies for our patients. This issue of Innovations in Cancer focuses on several points along this continuum, from bench research to supportive and integrative services to strengthen our patients.

Our cover feature focuses on our multidisciplinary effort to revolutionize the standard of care for prostate cancer, led by **Vikas Gulani, MD, PhD**, and **Lee Ponsky, MD**, and colleagues. Innovations in imaging are at the heart of the approach, including magnetic resonance fingerprinting (MRF). This technology, developed at Case Western Reserve University and UH, uses data derived from a standard MRI to instead describe the properties of tissues. Our prostate cancer team is already using MRF with select prostate cancer patients. They believe this and other technologies are rewriting the rules of the disease, putting us tantalizingly close to dramatically reducing unnecessary biopsies, procedures and treatments against low-grade tumors.

This issue of Innovations in Cancer also highlights our ongoing research into blood cancers. **David N. Wald, MD, PhD**, and **Marcos de Lima, MD**, have discovered why natural killer (NK) cells

are weaker and reduced in number in patients with acute myeloid leukemia (AML). In a series of experiments published in the journal Nature Communications, they've traced NK cell impairment among these patients to overexpression of glycogen synthase kinase (GSK) 3 beta protein – potentially opening up a new treatment avenue for AML. At the same time, their colleague **Lalitha Nayak, MD**, has explained why the cancer drug bortezomib decreases the risk of clotting – making it relatively unique among antineoplastic agents. She's traced the effect to Kruppel-like factor 2 (KLF2), finding that even very low doses of bortezomib increase clotting time by increasing KLF2. This discovery could lead to novel interventions to reduce risk of clotting, as well as ways to use KLF2 as a biomarker for clotting risk.

On the patient care side, we focus on our new Director of Supportive & Integrative Oncology, **Richard T. Lee, MD**, who recently joined the UH Seidman Cancer Center team from M.D. Anderson Cancer Center. Dr. Lee believes that as aggressive and innovative as we are with our traditional cancer therapies, we need to be just as aggressive with our supportive care services. And we highlight new evidence on the benefits of tomosynthesis from **Donna Plecha, MD**, recently published in JAMA. She and her colleagues have

found that adding tomosynthesis to traditional digital mammography increases invasive cancer detection and reduces recall rates for all women, regardless of breast density. This new technology may be reaching a tipping point.

Excellence in cancer care remains our focus. We are committed to providing the best in screening and prevention, developing the best new treatments, and discovering new approaches to manage and cure these difficult diseases. Join us by learning more about UH Seidman Cancer Center.

Warm regards,



STANTON L. GERSON, MD

Director, UH Seidman Cancer Center

*Director, Case Comprehensive Cancer Center
at Case Western Reserve University*

Asa and Patricia Shiverick – Jane Shiverick (Tripp)

*Professor of Hematologic Oncology,
Case Western Reserve University School of Medicine*



Cleveland | Ohio



The commitment to exceptional patient care begins with revolutionary discovery. University Hospitals Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a national leader in medical research and education and consistently ranked among the top research medical schools in the country by U.S. News & World Report. Through their faculty appointments at Case Western Reserve University School of Medicine, physicians at UH Case Medical Center are advancing medical care through innovative research and discovery that bring the latest treatment options to patients.

REPURPOSING BORTEZOMIB

Widely used drug's unconventional effect reveals potential anticlotting avenue

It's well-known that cancer patients are at increased risk of developing blood clots, both by virtue of the disease itself and because of treatment with antineoplastic agents. Research suggests that people with cancer have between four and seven and a half times the risk of developing a venous thromboembolism, when compared with the general population. Unfortunately, current anticoagulation therapies pose a significant risk of bleeding, all but eliminating them for consideration as a preventive strategy for these patients.

"Among pancreatic cancer patients, for example, almost 40 percent will develop a clot, but we don't know how to accurately predict the risk," says **Lalitha Nayak, MD**, a hematologist at University Hospitals Seidman Cancer Center. "Plus, the risks of anticoagulants are so high in these patients that we can't justify using them in a preventive way."

Research in Dr. Nayak's lab, however, may be changing this calculus. In cell and animal experiments using the cancer drug bortezomib, she and her colleagues have explained why this particular agent decreases the risk of clotting. The biochemistry behind this discovery, she says, could point to a new strategy for anticoagulation, as well as a potential biomarker for predicting clotting risk.

"We've known that multiple myeloma patients receiving bortezomib have a dramatically lower risk of clotting," she says. "This was a very important observation, but people couldn't explain why. By titrating bortezomib down to very low doses, we've found that it has a beautiful anticlotting effect, independent of any decrease in cell numbers. This effect is dependent on the transcription factor Kruppel-like factor 2 (KLF2). Bortezomib increases clotting time by increasing KLF2, without increasing the risk of bleeding."

Dr. Nayak's research is funded, in part, by a grant from the National Heart, Lung and Blood Institute to Case Western Reserve University School of Medicine. She and her colleagues have published their findings in the journal *Blood*.

According to Dr. Nayak, this discovery could have implications not only for cancer patients, but also for the millions of patients with other conditions who are at risk of developing blood clots.

"There are many, many conditions that increase clotting risk, not just cancer," she says. "Most of these diseases do not have an adequate therapeutic option. At the same time, there are many things that alter thrombosis, but if you don't understand how it works, it's hard to take things to clinical trials."

For the first time, we've been able to show that this huge effect we're seeing is due to KLF2. This shows us that KLF2 can be manipulated. Altering KLF2 levels might be a new way to alter the risk for clots. What's exciting is that bortezomib creates this effect at such low doses, we may not see the side effects we'd normally see."

Dr. Nayak is currently monitoring KLF2 levels in pancreatic cancer patients to test its potential as a biomarker for clotting risk. She's also exploring using KLF2 monitoring in patients with antiphospholipid antibody syndrome.

"We're looking to see what happens to patients' KLF2 levels over time," she says. "If we can correlate KLF2 levels with clotting, we might be able to institute anticoagulation therapy with bortezomib at certain quantifiable KLF2 levels. Right now, we wait for patients to clot, and then we treat them. They're in pain, they already have the clot, and, for cancer patients, we have to hold chemotherapy, which causes a lot of problems. Prevention would be so great. If we could have a drug that decreases the risk for clotting, without altering our bleeding risk, with very low side effects, that would be huge. Bortezomib may be that drug. It may not be an anticancer agent but an anticlotting agent at a very low dose, where it has a totally different effect. That's where I envision this going."

For more information on this research, email Dr. Nayak at Lalitha.Nayak@UHhospitals.org.



LALITHA NAYAK, MD

*Hematologist, UH Seidman Cancer Center
Assistant Professor of Medicine,
Case Western Reserve University
School of Medicine*

THE PROSTATE PROJECT

In a world where medicine is becoming increasingly precise, prostate cancer remains a stubborn outlier. Screening methods are bogged down in controversy, which is confusing for both physicians and their patients. For many physicians, diagnosing the condition can almost feel like a shot in the dark.

“The prostate is truly the last organ in the body that we are biopsying without hitting a visualized target,” says **Lee Ponsky, MD**, Chief of the Division of Urologic Oncology with University Hospitals Seidman Cancer Center. “There have been some advances in how we treat certain cases, but prostate cancer has been relatively stagnant over the past 20 years.”

Impatient with the pace of progress, a team of physicians and scientists at UH is working to alter that reality – and not just with incremental improvements around the edges. The multidisciplinary team of urologists, radiologists, radiation oncologists, medical physicists, pathologists and biomedical engineers is well on its way to establishing a new, disruptive model of care.

“It’s a ‘leave your egos at the door’ approach,” says UH radiologist **Vikas Gulani, MD, PhD**, Director of Magnetic Resonance Imaging. “Our goal is to form a multidisciplinary clinic in which the patient gets imaged and we come up with a diagnosis and treatment plan, ideally on the same day, eliminating the uncertainty that can carry on for weeks on end.”

“We have a clear vision together to make this happen, to make it clinically relevant and clinically impactful,” Dr. Ponsky adds. “It’s wonderful to discover new technologies. But we want to move the needle. We want to make a monumental impact, and that’s what we’re working to do.”

Innovations in prostate imaging are at the heart of the approach.

“We’re using all the tools at our disposal to change how prostate imaging is done,” Dr. Gulani says. “That includes current state-of-the-art MRI, developing screening methods with MRI, developing MR fingerprinting technology and developing advanced image analytics with the help of

biomedical engineering. We want to achieve the goal of reducing the uncertainty and reducing the number of unnecessary biopsies, procedures and treatments against low-grade cancer.”

The team has already developed a rapid, noncontrast screening exam that they have used in more than 100 research cases. This exam, which does not require an IV and is performed in under 15 minutes on the MR table, has an extremely high negative predictive value for prostate cancer in patients who ordinarily would have gone straight to nontargeted biopsy. In patients who have a suspicious focus on the MRI, a biopsy can be targeted at the suspicious area using one of several approaches available.

The team has also used magnetic resonance fingerprinting (MRF) in about 150 prostate cancer patients to date. This new technology, developed at Case Western Reserve University and UH and reported in the journal *Nature* in 2013, adds a quantifiable, reproducible aspect to traditional MR. It uses highly unusual and novel MR signal acquisitions to generate simultaneous measurements of multiple tissue properties for each pixel in the image, yielding quantitative maps of these tissue properties. These maps are used to noninvasively and definitively characterize tissue – both normal and abnormal. The application to prostate cancer is one of the earliest clinical uses of this technology. The hope is to provide a quantitative separation of prostate cancer from normal prostatic tissue, and perhaps even provide an estimate of the aggressiveness of the cancer.

Dr. Gulani is pleased to see the pioneering work in MR physics start to move to the clinical setting.

“We develop technology for the sake of helping patients, and I am really excited to move our work to this all-important stage of application,” he says.

Case Western Reserve University, UH Case Medical Center and Siemens Healthcare recently announced an exclusive research partnership to further refine and develop MRF. But already, the approach is yielding dividends for prostate cancer patients.

Multidisciplinary team at UH aims to disrupt traditional model of care

Beyond MRF, advances in engineering technology are also part of the approach. Anant Madabhushi, PhD, Professor of Biomedical Engineering at Case Western Reserve University, has worked to develop technology that aligns MRI and transrectal ultrasound-guided (TRUS) imagery without manual intervention. This MAPPER (Multiattribute Probabilistic Prostate Elastic Registration) technology has been shown to increase the yield of cancer-positive biopsies. Dr. Madabhushi is also collaborating with the clinicians to overlay pathological information from prostate tumors with data acquired using MRF.

“The idea is that computers can analyze MRI images and extract quantitative information about the structures in the images. Then we can input the pathological data from the patient’s tumor after surgery, including measurements of the texture of the cancer,” Dr. Ponsky says. “By fusing this information, the computer can then learn to recognize cancer. This is revolutionary.”

Another goal of the prostate group at UH is exploring cost-effectiveness, especially when it comes to MRI.

“Diagnostic MRI and MRI-guided biopsy have been shown to be effective in detecting clinically significant prostate cancer,” Dr. Gulani says. “However, despite the advantages, there is reluctance to incorporate MRI into standard practice because it is perceived to be expensive.”

New data from the UH-Case Western Reserve School of Medicine prostate team challenges this perception. The group compared cognitive MRI-guided biopsy, ultrasound-MR fusion or in-gantry MRI with standard prostate biopsy, presenting its findings at the recent meeting of the American Urological Association.

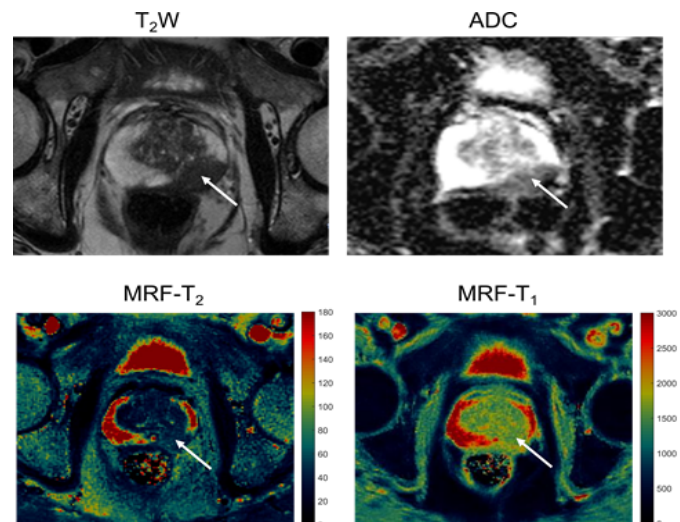
“Contrary to the knee-jerk reaction many people have, we found through careful analysis that MR prior to biopsy is actually cost-effective in the patient’s care,” Dr. Gulani says. “This is a very important fact, given the present state of discussion of our health care system. Whatever the costs of prostate cancer care are today, they are set to just skyrocket in the next 10 years. To be successful requires paying attention

to the totality of the question, including avoiding costs, overdiagnosis and overtreatment.”

For their part, Dr. Gulani and Dr. Ponsky say they are committed to disrupting the current model of care for prostate cancer, attacking its shortcomings from every angle.

“It’s a commitment to conferencing every week, reviewing our cases, talking with radiologists and urologists, and trying to improve our ability to interpret every day,” Dr. Ponsky adds. “We’re coming at this from all aspects and building a huge foundation that will allow us to change how we practice for prostate cancer. We think we have the tools to do it.”

For more information on prostate cancer screening, diagnosis and treatment at UH Seidman Cancer Center, email Vikas.Gulani@UHhospitals.org or Lee.Ponsky@UHhospitals.org.



STRONGER Together

New Supportive & Integrative Oncology Program at UH wants all hands on deck

RICHARD T. LEE, MD

*Director of Supportive & Integrative Oncology,
UH Seidman Cancer Center*

*Associate Professor of Hematology and Oncology,
Case Western Reserve University School of Medicine*

Parker Hannifin-Helen Moss Cancer Research Foundation

*Professor of Integrative Oncology,
Case Comprehensive Cancer Center
at Case Western Reserve University*

Imagine if every patient fighting cancer were optimally equipped to fight the disease, each person drawing on his or her unique strengths with the help of evidence-based health-promoting strategies. That's the vision behind the new Supportive & Integrative Oncology Program at University Hospitals Seidman Cancer Center.

"Usually when we think about cancer patients, we think about sick patients and attacking the cancer," says hematologist and oncologist **Richard T. Lee, MD**, who recently left M.D. Anderson Cancer Center in Houston to lead the new UH Seidman Cancer Center program. "What we're suggesting is a paradigm shift. Can we transform the patient from a passive sick person and instead create a healthy, strong individual who is also helping to fight the cancer? We've been very successful with all our traditional cancer therapies. We need to be just as aggressive with our supportive care services."

Integral to the new program is a multidisciplinary, coordinated approach to providing care. Using a biopsychosocial model, the Supportive & Integrative Oncology Program will incorporate everything from nutrition and exercise to chaplaincy, psychology and social work – to name just a few services.

"It's not just having all these services available to patients, but coordinating them in a way that makes them one unified program," Dr. Lee says. "Another interesting piece will be integrative medicine, where we'll bring in nonpharmacologic approaches, such as acupuncture, meditation, music therapy and massage therapy, to work together with conventional therapies to provide more options for patients."

Dr. Lee and his team are in the process of establishing evidence-based care pathways to help guide how supportive and integrative services are recommended and provided to patients.

"We need to be clear about how we're going to help support patients, from diagnosis through treatment and

into survivorship," he says. "If the patient has severe pain, which resources should he or she be considered for? How are we going to provide them?"

"The key is to focus on those services that have the most scientific data to support their use for specific indications. Just as we wouldn't give chemotherapy to everyone and we'd only give certain types of chemotherapy to certain patients, it's the same thing with acupuncture or meditation. The goal is to create something beyond the 'spa' approach, instead building supportive and integrative services into the spectrum of care that exists, with the aim of amplifying their effect by delivering them as part of a cohesive program."

To more fully build supportive and integrative services into patient care, Dr. Lee and his colleagues are planning a supportive care board, similar to a tumor board, to discuss challenging patient cases. His team will also be active in research, pursuing natural product drug discovery and launching clinical trials involving acupuncture and meditation.

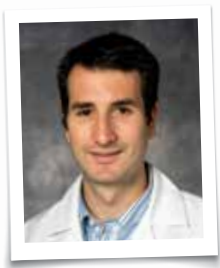
In taking on this new role at UH, Dr. Lee will be drawing on his experience at M.D. Anderson, where he most recently served as Associate Professor of Palliative, Rehabilitation and Integrative Medicine and Medical Director of the Integrative Medicine Program. Dr. Lee is a graduate of George Washington University, with dual degrees in anthropology and medicine. He completed his internal medicine residency at Stanford University, followed by a Fulbright scholarship to study traditional Chinese medicine and acupuncture at China Medical University Hospital in Taiwan and fellowship training in both hematology and medical oncology at the University of Chicago, where he served as chief fellow. Additionally, he completed a fellowship in palliative medicine at Northwestern University.

Dr. Lee says he's looking forward to meeting the challenges posed by his new position at UH, with the goal of improving patient care and quality of life.

"Our patients need support, but how do we best provide it?" he asks. "By building an infrastructure to bring all services together, it will naturally create more interactions and greater coordination, leading to a more unified approach, which is all to the benefit of patients."

To learn more about the Supportive & Integrative Oncology Program at UH Seidman Cancer Center, contact Dr. Lee at Richard.Lee3@UHhospitals.org.

Diagnosing Dysfunction



DAVID N. WALD, MD, PHD

Clinical Pathologist, UH Case Medical Center
and UH Rainbow Babies & Children's Hospital
Assistant Professor of Pathology and Medicine,
Case Western Reserve University School of Medicine



MARCOS DE LIMA, MD

Director, Hematologic Malignancies
and Stem Cell Transplant Program,
UH Seidman Cancer Center
Professor of Medicine,
Case Western Reserve University
School of Medicine

As a treatment for acute myeloid leukemia (AML), natural killer (NK) cells show encouraging potential. Because these cells are highly active in killing cancer, researchers have focused on methods of expanding donor cultures to be used in therapy. However, the specific characteristics of NK cells among AML patients have presented barriers to developing effective treatments.

"NK cells in AML patients are known to have reduced cytotoxic activity and be reduced in number," says **David N. Wald, MD, PhD**, a clinical pathologist at University Hospitals Seidman Cancer Center and UH Rainbow Babies & Children's Hospital.

Now, however, Dr. Wald and a team of colleagues have revealed a reason for this dysfunction, potentially opening up a new treatment avenue for AML patients. In a series of experiments, they've shown that NK cell impairment among AML patients can be traced to overexpression of glycogen synthase kinase (GSK) 3 beta protein.

"We've found that GSK3 beta protein levels are upregulated in NK cells from AML patients, when compared with cells from normal donors," Dr. Wald says. "This impairs their ability to kill AML cells. At the same time, we've also shown that inhibiting GSK3 expression in NK cells, either genetically or pharmacologically, enhances their cytotoxic activity."

The researchers reported their findings recently in the journal *Nature Communications*.

Although GSK3 has previously been shown to be a promising target in AML, the protein's function within NK cells has been less clear, Dr. Wald says.

"This is the first study to identify the important role GSK3 overexpression plays in AML," he says. "Also, in contrast to previous studies, our findings demonstrate that GSK3 inhibition not only impacts AML cells directly, but also hyperactivates NK cells and leads to AML cell killing."

"These findings are exciting," adds **Marcos de Lima, MD**, Director of the Hematologic Malignancies and Stem Cell Transplant Program at UH Seidman Cancer Center and a co-author of the study. "Our group is also investigating other cell therapies in cancer involving NK cells, dendritic cells, mesenchymal stromal cells and T lymphocytes."

Dr. Wald and Dr. de Lima collaborated on this work with researchers from the Department of Pathology at Case Western Reserve University School of Medicine, Invenio Therapeutics and M.D. Anderson Cancer Center.

Importantly, the group's data show that there are several ways to inhibit GSK3 in NK cells. *In vivo* strategies do work. Study findings showed that NK cells from patients with high levels of lithium – a known but weak GSK3 inhibitor –

had increased cytotoxic activity. Genetic manipulation also was shown to be effective. NK cells in which the GSK3 protein was absent killed 30 to 40 percent of tumor cells, as compared with 10 to 15 percent killed by wild-type NK cells. Experiments in mice also showed that NK cells treated with GSK3 inhibitors were effective in killing leukemia cells.

For now, however, Dr. Wald and the team believe an *ex vivo* strategy holds the most promise.

"Pretreating NK cells with GSK3 inhibitors resulted in enhanced killing of AML cells," he says. "Importantly, this enhanced NK cell cytotoxic activity only involves a short *ex vivo* exposure to GSK3 inhibitors. Therefore, this strategy does not require a patient to be exposed to the high doses of GSK3 inhibitors that are necessary for potent kinase inhibition, as well as NK cell hyperactivation."

"Our study has revealed the role of GSK3 in NK cell function, but more importantly, it has established a new therapeutic strategy for AML," Dr. de Lima says. "The hyperactivated NK cells exhibit a significantly improved ability to kill AML cells in both cell and animal systems. Because hyperactivation only requires a short *ex vivo* treatment with a GSK3 inhibitor, translation of this strategy to the clinic should be rapid."

For more information on this work, email David.Wald@UHhospitals.org or Marcos.DeLima@UHhospitals.org.

Tomosynthesis: Is It Reaching a Tipping Point?

3-D mammography superior to traditional imaging for both dense-breasted and nondense-breasted women, JAMA study finds

Tomosynthesis first grabbed headlines two years ago. Writing in JAMA, researchers from 13 breast centers reported results of a large study of breast imaging exams, which included more than 280,000 digital mammograms and more than 170,000 digital mammograms with supplemental 3-D tomosynthesis.

"The bottom line was that with the addition of tomosynthesis, our detection of breast cancers improved substantially, while our recall rate decreased," says **Donna Plecha, MD**, Director of Breast Cancer Imaging at University Hospitals Seidman Cancer Center and one of the study's authors. "We were able to show a 41-percent relative increase in the invasive cancer detection rate for combined tomosynthesis and digital mammography, compared with digital mammography alone. In this study, we also saw a 15-percent relative decrease in call-backs using tomosynthesis, compared with 2-D digital mammography alone."

Now, new findings support the apparent superiority of tomosynthesis. Reporting again in JAMA, researchers reviewed the same data as used in the 2014 study. But this time they considered women's breast density as a factor.

"Currently, 24 states have laws mandating that women be notified about the implications of breast density," says Dr. Plecha, who is also an author of the new JAMA study. "However, it's not known which if any additional modalities should be recommended for women with dense breasts."

Results of the new study show that adding tomosynthesis to traditional digital mammography increased invasive cancer detection and reduced recall rates for all women, regardless of breast density.

"People may think that tomosynthesis is only for dense-breasted women, and that's not the case," Dr. Plecha says. "This large study shows that it's good for dense and nondense breasts. That's the bottom line."

Specifically, study results show that improvements with tomosynthesis were largest for women with heterogeneously dense breasts and those with nondense breasts of scattered fibroglandular densities.

"These two groups make up about 82 percent of all women," Dr. Plecha says. "Everyone benefits from tomosynthesis, but these groups benefit more than others."

"Tomosynthesis makes us better," she adds. "We're not only finding more cancers – we found 48 percent more invasive cancers in the dense-breasted women and 30 percent in the nondense women. We've also reduced the recall rate 14 percent and 13 percent. No other supplemental screening exam does both."

For more information about the advantages tomosynthesis may provide to your patients, please contact Dr. Plecha at Donna.Plecha@UHhospitals.org.



DONNA PLECHA, MD

*Director, Breast Cancer Imaging,
UH Seidman Cancer Center*

*Associate Professor of Radiology,
Case Western Reserve University
School of Medicine*



Innovations in Cancer Summer 2016

Contributors: Stanton L. Gerson, MD; Lalitha Nayak, MD; Vikas Gulani, MD, PhD; Lee Ponsky, MD; Richard T. Lee, MD; David N. Wald, MD, PhD; Marcos de Lima, MD; Donna Plecha, MD
Writer: Kelly Kershner **Designer:** Justin Brabander

Innovations in Cancer is published by University Hospitals for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient. UHhospitals.org © 2016 University Hospitals in Cleveland, Ohio. All rights reserved. Contents of this publication may not be reproduced without the express written consent of University Hospitals. SCC 00877